



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | | |
|---|--|--|---|
| (51) International Patent Classification ⁷ : C12N 15/12, 15/62, C07K 14/78, 19/00, C12N 15/861, 15/867, A61K 48/00, G01N 33/68 | | A1 | (11) International Publication Number: WO 00/68379 (43) International Publication Date: 16 November 2000 (16.11.00) |
| (21) International Application Number: PCT/US00/12392 | | 20878 (US). FELDMAN, Andrew [US/US]; 7713 Green-brook Drive, Greenbelt, MD 20770 (US). | |
| (22) International Filing Date: 5 May 2000 (05.05.00) | | (74) Agents: SPRATT, Gwendolyn, D. et al.; Needle & Rosenberg, P.C., 127 Peachtree Street, N.E., Atlanta, GA 30303-1811 (US). | |
| (30) Priority Data: 60/133,243 7 May 1999 (07.05.99) US | | (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). | |
| (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/133,243 (CON) Filed on 7 May 1999 (07.05.99) | | Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> | |
| (71) Applicant (for all designated States except US): THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852-3804 (US). | | | |
| (72) Inventors; and (75) Inventors/Applicants (for US only): LIBUTTI, Steven, K. [US/US]; 14013 Welland Terrace, North Potomac, MD | | | |

(54) Title: METHODS FOR TREATING TUMORS USING ANTIANGIOGENIC COMPOUNDS

(57) Abstract

This invention provides a compound comprising a recombinant nucleic acid encoding an antiangiogenic protein inserted within a viral nucleic acid, wherein the recombinant nucleic acid can be packaged in a virus particle and wherein expression of the recombinant nucleic acid encoding the antiangiogenic protein results in production of the antiangiogenic protein. The present invention also provides a method of delivering an antiangiogenic protein to a cell, delivering an antiangiogenic protein to a subject, and treating a tumor in a subject comprising administering a virus comprising a recombinant nucleic acid encoding an antiangiogenic protein inserted within the viral nucleic acid, wherein the recombinant nucleic acid can be packaged in a virus particle, and wherein expression of the recombinant nucleic acid encoding the antiangiogenic protein results in production of the antiangiogenic protein, thereby delivering the antiangiogenic protein to the cell.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|---------------------------------------|----|---|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Larvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | ML | Mali | TR | Turkey |
| BG | Bulgaria | HU | Hungary | MN | Mongolia | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MR | Mauritania | UA | Ukraine |
| BR | Brazil | IL | Israel | MW | Malawi | UG | Uganda |
| BY | Belarus | IS | Iceland | MX | Mexico | US | United States of America |
| CA | Canada | IT | Italy | NE | Niger | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NL | Netherlands | VN | Viet Nam |
| CG | Congo | KE | Kenya | NO | Norway | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NZ | New Zealand | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | PL | Poland | | |
| CM | Cameroon | KR | Republic of Korea | PT | Portugal | | |
| CN | China | KZ | Kazakhstan | RO | Romania | | |
| CU | Cuba | LC | Saint Lucia | RU | Russian Federation | | |
| CZ | Czech Republic | LI | Liechtenstein | SD | Sudan | | |
| DE | Germany | LK | Sri Lanka | SE | Sweden | | |
| DK | Denmark | LR | Liberia | SG | Singapore | | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/12392

A. CLASSIFICATION OF SUBJECT MATTER

| | | | | | |
|-------|------------|-----------|-----------|-----------|------------|
| IPC 7 | C12N15/12 | C12N15/62 | C07K14/78 | C07K19/00 | C12N15/861 |
| | C12N15/867 | A61K48/00 | G01N33/68 | | |

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------------------|
| X | WO 98 49321 A (LI HONG; LU HE; RAGOT THIERRY; YEH PATRICE; GRISCELLI FRANC; LEGRAND YV) 5 November 1998 (1998-11-05) | 1-5, 8, 11, 16-20, 23-37 |
| Y | page 2, line 17, paragraph -page 3, line 11 page 8, line 12 - line 23 page 11, line 22 -page 13, line 33 ----- -/- | 6, 9, 10, 13-15 |

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

24 August 2000

11/09/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Mandl, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/12392

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|--|
| X | TANAKA T. ET AL.: "VIRAL VECTOR-TARGETED ANTIANGIOGENIC GENE THERAPY UTILIZING AN ANGIOSTATIN COMPLEMENTARY DNA" CANCER RESEARCH, vol. 58, no. 15, 1 August 1998 (1998-08-01), pages 3362-3369, XP000857409 ISSN: 0008-5472 the whole document | 1-3, 8, 16-20, 23-37 |
| Y | WO 98 48834 A (SINAI SCHOOL MEDICINE ;NAT INST HEALTH (US)) 5 November 1998 (1998-11-05) page 17, line 11 - line 21 | 21, 22, 38, 39 |
| X | BRAMSON J. L. ET AL.: "Direct intratumoral injection of an adenovirus expressing Interleukin-12 induces regression and long-lasting immunity that is associated with highly localized expression of Interleukin-12" HUMAN GENE THERAPY, vol. 7, 20 October 1996 (1996-10-20), pages 1995-2002, XP002093895 ISSN: 1043-0342 the whole document | 1, 2, 11, 16, 18, 23-31 |
| X | CRYSTAL R. G. : "The body as manufacturer of endostatin." NATURE BIOTECHNOLOGY, vol. 17, April 1999 (1999-04), pages 336-337, XP002145429 cited in the application the whole document | 1-5, 8, 12, 16-19, 23-31 |
| X | TANAKA T. ET AL.: "Viral vector-mediated transduction of a modified platelet factor 4 cDNA inhibits angiogenesis and tumor growth." NATURE MEDICINE, vol. 3, no. 4, 1997, pages 437-442, XP002145430 ISSN: 1078-8956 the whole document | 1-3, 5, 8, 12, 16-20, 23-31, 37 |

-/-

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 00/12392

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|----------------------------|
| X | BLEZINGER P. ET AL.: "SYSTEMIC INHIBITION OF TUMOR GROWTH AND TUMOR METASTASES BY INTRAMUSCULAR ADMINISTRATION OF THE ENDOSTATIN GENE" NATURE BIOTECHNOLOGY, vol. 17, no. 4, April 1999 (1999-04), pages 343-348, XP000857410 ISSN: 1087-0156 cited in the application the whole document | 37 |
| Y | — | 1-5, 8, 16-20, 23-36 |
| X | WO 97 16169 A (CHIRON CORP) 9 May 1997 (1997-05-09) | 37 |
| Y | the whole document | 1-5, 8, 16-20, 23-36 |
| Y | SCHWARZ M. ET AL.: "EMAP II: A modulator of neovascularization in the developing lung." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 20, no. 2, February 1999 (1999-02), pages L365-L375, XP002145431 ISSN: 1081-5589 the whole document | 6 |
| Y | PIKE S. E. ET AL.: "Vasostatin, a calreticulin fragment, inhibits angiogenesis and suppresses tumor growth." JOURNAL OF EXPERIMENTAL MEDICINE, vol. 188, no. 12, 21 December 1998 (1998-12-21), pages 2349-2356, XP002145432 ISSN: 0022-1007 column W | 9 |
| Y | WO 97 34586 A (TSIARAS WILLIAM G ;SPEAR PETER D (US); BAETGE E EDWARD (US); CYTOT) 25 September 1997 (1997-09-25) page 9, paragraph 2 | 10 |
| Y | SHUTTLEWORTH C. A.: "Type VIII collagen." INTERNATIONAL JOURNAL OF BIOCHEMISTRY & CELL BIOLOGY, vol. 29, no. 10, October 1997 (1997-10), pages 1145-1148, XP000938722 ISSN: 1357-2725 the whole document | 13 |
| | — | —/— |

INTERNATIONAL SEARCH REPORT

| | |
|-----------------|-----------------------|
| Int'l | Serial Application No |
| PCT/US 00/12392 | |

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|---|
| Y | <p>RAMCHANDRAN R. ET AL.: "Antiangiogenic activity of restin, NC10 domain of human collagen XV: Comparison to endostatin." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 255, no. 3, 24 February 1999 (1999-02-24), pages 735-739, XP002145434 ISSN: 0006-291X the whole document</p> <p>—</p> | 14 |
| Y | <p>RAMCHANDRAN R. ET AL.: "Cloning, expression of a novel anti-angiogenic protein: Restatin." PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 40, March 1999 (1999-03), page 620 XP000938553 ISSN: 0197-016X the whole document</p> <p>—</p> | 15 |
| P, X | <p>SAUTER B. V. ET AL.: "Adenovirus-mediated gene transfer of endostatin in vivo results in high level of transgene expression and inhibition of tumor growth and metastases." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 97, no. 9, 25 April 2000 (2000-04-25), pages 4802-4807, XP002145436 April 25, 2000 ISSN: 0027-8424 the whole document</p> <p>—</p> | 1, 2, 4, 16, 18, 20, 23-31, 37 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/12392

| Patent document cited in search report | Publication date | Patent family member(s) | | | Publication date |
|--|------------------|-------------------------|--------------|------------|------------------|
| WO 9849321 | A 05-11-1998 | AU 7909698 | A 24-11-1998 | CN 1254378 | T 24-05-2000 |
| | | EP 0979290 | A 16-02-2000 | NO 995242 | A 27-12-1999 |
| | | ZA 9803553 | A 04-02-1999 | | |
| WO 9848834 | A 05-11-1998 | AU 7471098 | A 24-11-1998 | | |
| WO 9716169 | A 09-05-1997 | AU 7525296 | A 22-05-1997 | AU 7527596 | A 22-05-1997 |
| | | EP 0858322 | A 19-08-1998 | WO 9716170 | A 09-05-1997 |
| WO 9734586 | A 25-09-1997 | US 5904144 | A 18-05-1999 | AU 716400 | B 24-02-2000 |
| | | AU 2541997 | A 10-10-1997 | EP 0927024 | A 07-07-1999 |
| | | JP 2000507854 | T 27-06-2000 | | |